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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/115,589	07/15/1998	JENNIFER E. VAN EYK	12917	1553

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EXAMINER	
GUCKER, STEPHEN	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/115,589	VAN EYK ET AL.	
	Examiner	Art Unit	
	Stephen Gucker	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22-28 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22-28 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/21/04 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because claims 23-24 and 26-27 recite specific portions of an amino acid sequence by numbered residues, but do not include unique sequence identifiers (SEQ ID NOs). Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Applicant is given THREE MONTHS from the mailing date of this communication within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the

application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

5. Applicant should review the instant Application in its entirety for compliance with the sequence rules, paying particular attention that all sequences recited throughout the disclosure in its entirety have SEQ ID NOs and that the SEQ ID NOs recited are found in both the CRF and paper copy of the Sequence Listing. Applicant must comply with the sequence rules and the remainder of the entire Office action simultaneously. Otherwise, the applicant will receive a Notice of Non-Responsive Reply.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7, 15-20, 28, and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods employing HPLC and mass spectrography or using a compound which specifically binds to the peptide fragment or the myofilament protein or covalent or non-covalent complex formation comprising a peptide fragment of a myofilament protein under conditions which allow the compound to form a complex with the peptide fragment of the myofilament protein or covalent or non-covalent complex formation comprising a peptide fragment of a myofilament protein (i.e., this is the language of claim 8), does not reasonably provide enablement for methods which do not employ HPLC and mass spectrography or that lack any compound that specifically binds to the peptide fragment etc. (i.e., language of claim 8).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. After further extensive literature review, the Examiner cannot find evidence of any method in the prior art that measures peptide fragments of myofilament proteins or their covalent or non-covalent complexes that does not employ HPLC or a compound which specifically binds to the peptide fragments or their covalent or non-covalent complexes. Such prior art methods always use HPLC or the compounds recited in the Markush group of instant claim 9 (antibodies, fragments of antibodies, proteins, fragments of proteins, peptides, or peptidomimetics). The specification lacks any working or even prophetic examples that do not employ HPLC or a compound which specifically binds. The specification also does not provide any guidance as to what methods could be employed that do not use HPLC or compounds that specifically bind under the appropriate conditions. Without such a teaching or disclosure in the prior art or the specification, even the most skilled of artisans could not reasonably make and use the invention to the full reasonable scope of the claims because it is entirely unpredictable as to what process steps and reagents would be required for such broad methods which are not limited to any specifically recited process steps or reagents.

8. Claims 1-7, 15-20, 28, and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. The specification is silent in regards to methods that do not employ HPLC or compounds that specifically bind.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-7, 15-20, 28, and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Unlike instant claim 8 and the claims dependent on instant claim 8, these claims recite "a method of assessing muscle damage in a subject, comprising evaluating..." without a recitation of the specific process steps taken in order to do the evaluating. Without a recitation of the specific process steps involved in the evaluating, the metes and bounds of the claims are indefinite because it cannot be determined what is specifically encompassed by the method of evaluation, i.e. an act of mental computation, a sensory determination based on visual inspection, smell, or taste, a process that uses scientific reagents and/or equipment, etc.

11. Claims 23-24 and 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite specific amino acid sequences by specific amino acid numbers without reciting a unique SEQ ID NO. Without the recitation of a SEQ ID NO, the metes and bounds of the claims are indefinite because different conventions exist as to the exact numbering of protein sequences, e.g. some numbering methods count the signal sequence, certain pre- or

pro- amino acid regions, N-terminal methione residues added by recombinant bacteria, while others do not, etc. Also, it cannot be determined from the claims what species form of the proteins the numbering refers to (human? canine? rat?), how alternate splice variants or allelic variants of the proteins recited should be numbered, etc., and this adds to the vagueness of the instant claims.

12. Claims 1-13, 15-20, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Löfberg et al. ("Löfberg"). Löfberg discloses the use of various antibodies and detectable labels and markers (iodine-125, antibodies conjugated to solid-phase magnetic particles, and immunoenzymometric assays, page 1211) to detect two different fragments of myosin heavy-chain, troponin I, and troponin T for the purpose of assaying acute muscle damage, irreversible cardiac and skeletal muscle damage, and reversible skeletal muscle damage from biological samples such as serum (pages 1211-1212). Although the troponin proteins measured by Löfberg may not be true fragments as the myosin heavy-chain fragments are, the troponin proteins measured by Löfberg meet the instant claim limitations for several reasons. First, the claims use open language when referencing peptide fragments, such as "comprising a peptide fragment", such that the claims encompass non-fragmented troponin proteins which do indeed "comprise" a peptide fragment of a troponin protein. The grounds of this part of the rejection could be obviated by the use of "consisting of" language in reference to "peptide fragments." Second, the specification broadly defines "complex formation comprising a peptide fragment of a myofilament protein" to include a peptide bound to an antibody. When an antibody binds to a troponin protein as it does in the Löfberg

reference, it meets the limitations of a "complex formation comprising a peptide fragment of a myofilament protein." Löfberg meets all the claim limitations, including assaying serum for different fragments or epitopes from myosin heavy-chain (same protein), and comparing such with serum levels of troponin T and troponin C (different proteins, page 1212) and measuring amounts over time and constructing ratios (page 1213 and Figures 1 and 2) to indicate the extent of muscle damage (how long the damage lasted over time, whether it involved skeletal muscle, cardiac muscle, or both, etc.).

13. Claims 1-13, 15-20, 22, 28 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Westfall et al. ("Westfall"). Westfall discloses the use of various antibodies and detectable markers (alkaline phosphatase, page 303) to detect fragments from both troponin I and troponin T (abstract) for the purpose of assaying cardiac muscle damage from ischemia from biological samples such as a component of cardiac muscle tissue (page 303). The amount of damage is correlated with time of ischemia (30 minutes as compared to 60 minutes) and ratios were established between the gradual reduction of whole troponins and the appearance of troponin fragments (pages 307-308, Figures 10 and 11, and Table 1).

14. Claims 1-4, 6-20, 22-24, 28, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Wicks et al. (WO 94/27156, "Wicks") for reasons of record and the following. Wicks discloses the use of antibodies and detectable labels and markers (enzymes, alkaline phosphatase, page 12) to detect troponin I (and specific fragments claimed, page 5 and claims 12-13, 18, 26-27, 32-34, and 36) and troponin C in a

complex in sandwich assays having immobilized solid phases for the purpose of assaying irreversible cardiac damage from biological samples such as blood (pages 2-5).

Applicant's arguments filed 4/19/01 have been fully considered but they are not persuasive because Applicant argues that a method for assessing muscle damage in a subject by evaluating for the presence or absence of a "**myofilament protein modification product**" as defined by the instant specification is absent from Wicks. The specification defines the phrase "myofilament protein modification product" very broadly, such that it encompasses multiple proteins (troponin I, troponin T, troponin C, myosin light chain 1, α-actin, etc.) and all fragments of these proteins, in addition to covalent or non-covalent complexes of two or more intact proteins or any fragments of these proteins. Furthermore, the phrase also encompasses covalent or non-covalent complexes of any myofilament protein or any fragment thereof with any other non-myofilament protein or any fragment thereof (see page 10, line 21 to page 11, line 15). The Examiner maintains that Wicks meets all the limitations of the claims when he teaches methods to detect troponin I and troponin C in a complex because any complex formation, covalent or non-covalent, is encompassed by the instant claims as defined by the phrase "myofilament protein modification product" as defined by the instant specification. Contrary to Applicant's assertion, Wicks is drawn to methods of detecting muscle (cardiac) damage, see pages 1-2 of Wicks, especially page 2, lines 11-16. Wicks teaches detecting troponin I and his methods can detect different fragments of troponin I, meeting the claim limitations of two different myofilament protein modification

products because the broad phrase encompasses two different fragments as defined by the instant specification. The methods of Wicks using antibodies raised against troponin I fragments would inherently detect the fragments themselves, again meeting the broad limitations of the claims. The use of the antibodies and processes of Wicks inherently meets all claim limitations, even if the intent is not to detect cardiac troponin I fragments per se (Ex parte Novitski, 26 USPQ 1391).

Applicant's arguments filed 12/1/03 have been fully considered but they are not persuasive because Applicant argues that Wicks does not teach detection of a peptide fragment of a myofilament protein or detection of a covalent or non-covalent complex comprising a fragment of a myofilament protein. However, the claims use open language when referencing peptide fragments, such as "comprising a peptide fragment", such that the claims encompass non-fragmented troponin proteins which do indeed "comprise" a peptide fragment of a troponin protein. The grounds of this part of the rejection could be obviated by the use of "consisting of" language in reference to "peptide fragments." The specification broadly defines "complex formation comprising a peptide fragment of a myofilament protein" to include a peptide bound to an antibody. When an antibody binds to a troponin protein as it does in the Wicks reference, it meets the limitations of a "complex formation comprising a peptide fragment of a myofilament protein," so Wicks does meet all the claim limitations.

15. Claims 1-2, 8-20, 25-28, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Takahashi et al. (WO 96/10078, "Takahashi") for reasons of record and the following. Takahashi discloses the use of antibodies and detectable labels and

markers (enzymes, peroxidase and alkaline phosphatase, pages 6-7 and 9) to detect myosin light chain 1 (MLC-1) in a complex in sandwich assays having immobilized solid phases (pages 10 and 12) for the purpose of assaying cardiac damage from biological samples such as blood (pages 2-5).

Applicant's arguments filed 4/19/01 have been fully considered but they are not persuasive because Applicant argues that a method for assessing muscle damage in a subject by evaluating for the presence or absence of a "**myofilament protein modification product**" as defined by the instant specification is absent from Wicks. The specification defines the phrase "myofilament protein modification product" very broadly, such that it encompasses multiple proteins (troponin I, troponin T, troponin C, myosin light chain 1, -actin, etc.) and all fragments of these proteins, in addition to covalent or non-covalent complexes of two or more intact proteins or any fragments of these proteins. Furthermore, the phrase also encompasses covalent or non-covalent complexes of any myofilament protein or any fragment thereof with any other non-myofilament protein or any fragment thereof (see page 10, line 21 to page 11, line 15). Like Wicks, the use of the antibodies and processes of Takahashi would detect not only MLC-1, but fragments of MLC-1 from the amino terminal of MLC-1 because that is what the antibodies of Takahashi were raised against (see abstract). Takahashi inherently meets all claim limitations, even if the intent is not to detect cardiac MLC-1 fragments per se (Ex parte Novitski, 26 USPQ 1391).

Applicant's arguments filed 12/1/03 have been fully considered but they are not persuasive because Applicant argues that Takahashi does not teach detection of a

peptide fragment of a myofilament protein or detection of a covalent or non-covalent complex comprising a fragment of a myofilament protein. However, the claims use open language when referencing peptide fragments, such as "comprising a peptide fragment", such that the claims encompass non-fragmented myosin light chain proteins which do indeed "comprise" a peptide fragment of a myosin light chain protein. The grounds of this part of the rejection could be obviated by the use of "consisting of" language in reference to "peptide fragments." The specification broadly defines "complex formation comprising a peptide fragment of a myofilament protein" to include a peptide bound to an antibody. When an antibody binds to a myosin light chain protein as it does in the Takahashi reference, it meets the limitations of a "complex formation comprising a peptide fragment of a myofilament protein," so Takahashi does meets all the claim limitations.

16. No claim is allowed.

17. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technical Center 1600 general number which is (571) 272-1600.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (571) 272-0883. The examiner can normally be reached on Monday to Friday from 0930 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Kunz, can be reached at (571) 272-0887. The fax phone number for this Group is currently (703) 872-9306.

SG

Stephen Gucker

April 5, 2004

Gary d. Kunz

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